REMARKS

Claims 1 and 3-9 are pending in the present application.

The rejections of: (a) Claims 1-2 under 35 U.S.C. §102(b) over Gelfand et al and (b) Claims 3-5 under 35 U.S.C. §103(a) over Gelfand et al, are respectfully traversed.

The present invention provides, *inter alia*, an isolated L-leucine producing bacterium belonging to the genus *Escherichia* which produces L-leucine, L-valine, L-isoleucine and L-homoleucine, wherein the amount of L-valine, L-isoleucine, and L-homoleucine produced is less than 1% of that of L-leucine produced, due to inactivation of *ilvE* gene or decreasing activity of the protein encoded by *ilvE* gene. (see Claim 1)

In contrast, Gelfand et al fail to disclose or suggest the L-valine or L-homoleucine content of the bacterium disclosed therein. As stated above, the claimed invention requires that L-leucine, L-valine, L-isoleucine and L-homoleucine be expressed and that the amount of L-valine, L-isoleucine, and L-homoleucine produced is less than 1% of that of L-leucine produced. Therefore, the absence of a disclosure by Gelfand et al of a bacterium meeting this specific requirement would necessarily make this reference fail to anticipate the presently claimed invention.

It appears that it is the Examiner's position that Gelfand et al would inherently meet the concentration limitations. Specifically, the Examiner refers to DG31 and DG34 and alleges that these strains would anticipate the claimed invention because the ilvE gene is disrubpted.

Applicants direct the Examiner's attention to MPEP §2112, which states:

> "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17

USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)

In making the outstanding rejection, the Examiner has failed to provide a reasonable basis in fact and/or technical reasoning to support a determination of inherency. Specifically, the Examiner alleges that the fact that *ilvE* gene is disrupted would mean that the claimed relationship of the recited amino acids is met. However, in making this assertion the Examiner clearly overlooks the genotype description in Table 1 of Gefland et al. In Table 1, it is clearly stated that, in addition to transduction with *ilvE12*, strain DG31 also is transduced with *tyrA*$^+$. Also from this table, strain DG34 is transduced with *aspC13* and *ilvEl2*. In view of the foregoing, Applicants submit that the Examiner has failed to provide any evidence to support a determination of inherency.

In fact, it is well established that the doctrine of inherency is based on certainties, not possibilities or probabilities. As such, so long as there are any questions in the art as to the state of the materials disclosed in the cited art of record, then this rejection must fall. Applicants submit that such a statement does exist as it is not clear what role the presence of the ileE12 and aspC13 would in play the production levels of L-leucine, L-valine, L-isoleucine and L-homoleucine and the relationship between the same. In the absence of such as disclosures, Applicants submit that the presently claimed invention is not anticipated by Gelfand et al.

Applicants submit that the present invention would not even be obvious over Gelfand et al. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation... to modify the reference... Second, there must be a reasonable expectation of success. Finally, the prior art reference... must teach or suggest all the claim limitations." (MPEP §2142)

Applicants submit that the bacterium disclosed by Gelfand et al does not produce

L-leucine, L-valine, L-isoleucine and L-homoleucine, wherein the amount of L-valine, L-isoleucine and L-homoleucine produced is less than 1% the amount of L-leucine produced. Moreover, based on the disclosure of Gelfand et al, there is simply no disclosure of how the skilled artisan would produce and, therefore, the skilled artisan would not be able to produce a bacterium that produces L-leucine, L-valine, L-isoleucine and L-homoleucine, wherein the amount of L-valine, L-isoleucine and L-homoleucine produced is less than 1% the amount of L-leucine produced. Applicants submit that Gelfand et al would fail to render the present invention obvious even if the skilled artisan were to transform the bacterium disclosed therein with tyrB gene to overexpress said tyrB gene.

In view of the foregoing, Applicants request withdrawal of these grounds of rejection.

The rejections of Claims 1-5 under 35 U.S.C. §112, first paragraph (written description and enablement), are obviated in part by amendment and traversed in part.

The Examiner's criticizes the claimed invention and alleges that the claimed invention fails to describe and enable the scope of the invention claimed. Specifically, the Examiner's primary criticisms are that the specification fails to describe and enable the broad genus of modifications resulting in the claimed expression relationship between L-leucine, L-valine, L-isoleucine, and L-homoleucine, the specification fails to describe and enable the broad genus of genes encoding an aromatic amino acid aminotransferase and the broad genus of aromatic amino acid aminotransferases, the broad genus of means to inactivate the ilveE gene, and the broad genus of means of increasing activity of the tyrB gene product.

To address these criticism, Claim 1 has been amended recite the limitations of original Claim 2. In addition, Claim 3 has been amended to define the means for increasing activity of

the tyrB gene product to the following two means, "by increasing a copy number of said tyrB gene" or "by locating said tyrB gene under control of a potent promoter." This amendment is supported by the description on page 9, lines 14-20, and page 11, lines 1-4 of the specification.

In view of these amendments and contrary to the Examiner's allegations, Applicants submit that the specification fully describes and enables the scope of the claimed invention. Specifically, the specification teaches the skilled artisan how to make and use the claimed invention with sufficient particularity so as to enable the skilled artisan to practice the same without undue experimentation and to appreciate the metes and bounds of the claimed invention. Thus, Applicants submit that the claimed invention does comply with 35 U.S.C. §112, first paragraph.

At the outset, the Examiner is reminded that MPEP § 2163.02:

> An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989).

Applicants submit that the specification provides an adequate description to allow the skilled artisan to recognize what has been invented and what is claimed is adequately described in the specification within the meaning of 35 U.S.C. § 112, first paragraph.

Further, MPEP § 2164.01 states:

> The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.

Applicants submit that the skilled artisan would readily appreciate the full scope of the claimed invention and would be able to make and use the same without undue experimentation.

The bacterium of Claim 1 is a bacterium which produces L-leucine, L-valine, L-isoleucine and L-homoleucine, whereinthe amount of L-valine, L-isoleucine and

L-homoleucine produced is less than 1% the amount of L-leucine produced, due to inactivation of ilvE gene or decreasing activity of the protein coded by ilvE gene. Inactivation of ilvE gene can be performed not only by deletion mutation, but also by site-directed mutagenesis, homologous recombination, and insertion mutagenesis (see page 7, line 20 to page 8, line 2 of the specification). As such, one of ordinary skill in the art can readily perform these methods based on the sequence information of ilvE gene of E. *coli.*

In addition, as described on page 8; line 3-7 of the specification, method for decreasing activity of the protein coded by ilvE gene includes modification to the expression regulation sequence of ilvE gene, besides modification to the protein coding sequence of ilvE gene. One of ordinary skill in the art can readily find DNA sequences of expression regulation sequence of ilvE gene based on genome information, for example, by searching upstream region of ilvE gene in a genomic sequence disclosed in a public database.

Further, activity of the tyrB gene product can be increased not only by increasing the copy number of said tyrB gene, but also by locating said tyrB gene under control of a potent promoter, which is described on page 9, lines 14-20, and page 11, lines 1-4 of the specification.

Further, with respect to the sequences of the ilvE gene and the tyrB gene, and their corresponding gene products, the Examiner is reminded of the recent decision by the Federal Circuit in which the Court held that the "written description" requirement must be applied in the context of the particular invention and the state of the knowledge in the art (*Capon v. Eshhar*, 418 F.3d 1349, 76 USPQ2d 1078 (Fed. Cir. 2005)). In *Capon*, the Court held that the Board erred in holding that the nucleotide sequences of the chimeric genes must be fully presented, although the nucleotide sequences of the component DNA are known. The *Capon* Court further stated that when the prior art includes the nucleotide information, precedent does

not set a *per se* rule that the information must be determined afresh. Therefore, where a person experienced in the field of this invention would know that the DNA of the claims is well-known, there is no requirement to once again set forth these sequences.

To this end, the Examiner's attention is directed to page 7, lines 10-19 where the ilvE gene and gene product are described. Further, at page 7, lines 17-19, Applicants specifically describe the location of the ilvE gene in GeneBank accession number NC_000913.1, gi:16131628. Therefore, the identity of the ilvE gene and corresponding gene product are sufficiently described based on the state of the relevant art and, as such, it is not necessary for Applicants to recite the same in order to comply with the written description requirement.

Additionally, the Examiner's attention is directed to page 9, lines 1-13 where the tyrB gene and gene product are described. Further, at page 9, lines 11-13, Applicants specifically describe the location of the tyrB gene in GeneBank accession number NC_000913.1, gi:16131880. Therefore, the identity of the tyrB gene and corresponding gene product are sufficiently described based on the state of the relevant art and, as such, it is not necessary for Applicants to recite the same in order to comply with the written description requirement.

Based on the foregoing, Applicants submit that the present invention is sufficiently described and enabled as required by 35 U.S.C. §112, first paragraph.

Applicants request withdrawal of these grounds of rejection.

The rejection of Claims 4-5 under 35 U.S.C. §112, second paragraph, is obviated by amendment.

Claims 4-5 were rejected for failing to recite essential steps. Applicants have amended Claim 4 to recite the phrase "to increase the copy number of the DNA containing said *tyrB*

gene." Applicants submit that Claims 4 and 5 are now complete.

Withdrawal of this ground of rejection is requested.

The rejection of Claims 3-5 under 35 U.S.C. §112, second paragraph, is obviated by amendment.

Claim 3 has been amended to restrict the tyrB gene to Escherichia coli. Therefore, this ground of criticism by the Examiner is believed to be moot.

Withdrawal of this ground of rejection is requested.

The rejection of Claims 1-3 under 35 U.S.C. §101 is obviated by amendment. Claim 1 has been amended to define the L-leucine producing bacterium as being "isolated." Therefore, this ground of rejection is no longer believed to be relevant. Acknowledgement of withdrawal of this ground of rejection is requested.

The objection to Claim 1 is believed to be obviated by amendment. Applicants have amended Claim 1 in accordance with the Examiner's kind suggestion. As such, withdrawal of this ground of rejection is requested.

The objection to the specification is believed to be obviated by amendment. Applicants have amended the specification to address the specific criticisms raised by the Examiner. The specification has also been briefly reviewed for other errors that need to be corrected so as to provide clarity and notice to that which is claimed. Withdrawal of this ground of objection is requested.

Applicants submit that the present application is in condition for allowance. Early notice to this effect is earnestly solicited.

Respectfully submitted,

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